REMARKS

In the Final Action dated December 1, 2010, Claims 1-4, 6-8, 13 and 16-83 were pending. Claims 2-4, 6-8, 16-31 and 34-82 were withdrawn from consideration; however, the Examiner has acknowledged that claims 16, 32, 33 and 83 include subject matter that may be entitled to rejoinder. Claims 1, 13, 32, 33 and 83 were under examination to the extent that these claims read on SEQ ID NO: 7, and were rejected. The Examiner has again indicated allowable claim language.

In the foregoing amendments, claim 1 has been amended to improve the language and format. Claims 29-30 have been amended to delete references to canceled claims. New claim 83 has been added, as supported by original claim 1 and in consideration of the claim language indicated by the Examiner to be allowable. Withdrawn claims 2-4, 6-8, 17-18 and 34-82 have been cancelled, without prejudice or disclaimer. Applicants reserve the rights to pursue the subject matter of the canceled claims in one or more divisional applications.

No new matter is introduced. Entry of the amendments is respectfully requested.

Claim Objection

Claims 32, 33, and 83 were objected to because they recite non-elected subject matter in the alternative.

Applicants maintain that rejoinder of the additional combinations which require SEQ ID NO: 7 will be considered once the claims based on elected SEQ ID NO: 7 are found allowable. The Examiner has acknowledged that rejoinder will be considered when appropriate.

35 U.S.C. § 112, Second Paragraph Rejections

Claims 1, 13, 32, 33 and 83 were rejected under 35 U.S.C. §112, second paragraph as

indefinite for allegedly missing an essential step.

This rejection is obviated by the instant amendments to claim 1. Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 112, First Paragraph Rejection

Claims 1, 13, 16, 32, 33, and 83 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Examiner has indicated that the following subject matter is enabled and allowable:

> *A method for determining an increased likelihood of the presence of colorectal adenoma in a human, said method comprising*
>
> > *measuring the level of an mRNA which comprises the RNA equivalent of SEQ ID NO: 7 in a gastrointestinal tract sample from said human and*
> >
> > *determining an increased likelihood of the presence of colorectal adenoma when the level of said mRNA is increased in said human relative to the normal level of said mRNA in gastrointestinal tract samples from healthy individuals.*

However, the Examiner maintains that the specification does not provide enablement for methods which detect any other transcription or translation products (including a protein encoded by an mRNA which comprises the RNA equivalent of SEQ ID NO: 7), methods which utilize other samples, or methods for the positive detection of colorectal adenoma.

In particular, even though the Examiner has acknowledged that the applicant "has indeed established that instant SEQ ID NO: 7 is transcribed from a portion of the 'KIAA1199 gene' that has been considered an intron [by others]" (Office Action, page 14, lines 3-4), the Examiner has taken the position that it is unknown from the specification whether the "intronic mRNA" is actually translated, and whether the translation product is also present at different levels to be diagnostic of the onset of colorectal adenoma. Further, in the Examiner's view, the data in the

specification and the art do not support an assertion that an mRNA comprising the RNA equivalent of SEQ ID NO: 7 encodes the protein known in the art as KIAA1199. See, Final Action, pages 10-11 (bridging paragraph) and pages 13-15. The Examiner subjected instant SEQ ID NO: 7 to a six-frame translation analysis, and did not find any significant match with the protein sequence of KIAA1199. See middle to bottom of page 13 of the Action. Assuming that the mRNA molecules in question are translated into proteins, the Examiner states that the level of translation is not always concordant with the mRNA expression level.

Further, the Examiner has objected to the reliance of post-filing data in order to establish enablement for detecting protein levels and utilizing other sample sources. The Examiner has commented that it is not clear how much of the data relied upon from the NCBI databases were available to the skilled artisan (bottom of page 12 of the Action); and that the possible proteins (directly) encoded by SEQ ID NO: 7 has very little identity to KIAA1199 (middle of page 15 of the Action), and there is no evidence that the anti-KIAA1199 antibody, utilized in the experiments described in the declaration, was available at the time of filing (middle of page 15 and top of page 16 of the Action). Additionally, the Examiner has rejected our argument that the additional experimentation would be routine, and concludes that the art is highly unpredictable, as evidenced by the Chan reference and the Galamb reference (see pages 8 and 17 of the Action).

Applicants disagree. Applicants respectfully submit the following remarks and request that the Examiner reconsider and withdraw the enablement rejection.

SEQ ID NO:7 is part of the XM 051857.1 predicted Gene Locus (later named KIAA1 199)

a. Online tools available prior to the filing of the corresponding PCT application included Human database, Hg8 (August 2001) and NCBI Blast tools. Blasting the 3671 nt of

SEQ ID NO: 7 would result in a 99.8% identify hit to a predicted gene locus in Hg8 Chromosome 15, 82400000-8260000. The gene boundaries were defined by the longest identified cDNA clone, namely XM_051857.1.

b. The sequence of SEQ ID NO: 7 aligned in between exon 1 and 2 of the XM_051857.1 clone.

c. As four other cDNA clones were included in the predicted XM 051857.1 clone which demonstrated other exonic regions outside the XM_051857.1, it would have been reasonable for a person skilled in the art to conclude that SEQ IDNO: 7 was a cDNA clone representing a novel exon of the gene defined by the boundaries of XM_051857.1.

It is noted that there seems to be some confusion in relation to what the Examiner understands is meant by the term "exons". An exon is a region which forms part of the messenger RNA. It can include both translated and untranslated sequence. As you know, mRNA is an assembly from exons from which the introns have been excised. Nevertheless, mRNA does still include both 5' and unprimed translated regions. Since mRNA is only composed of exons, these untranslated regions form part of the exons at either end of the transcript. There is no doubt that SEQ ID NO: 7 formed part of an mRNA transcript since it was identified from mRNA and therefore was inherently forming part of an exon region.

d. The human Genome project was 1 year old in 2001. Gene mapping was obtained by piecing cDNA clones together as they appeared. Obtaining full length cDNA sequences required multiple ESTs which were then pieced together.

e. Further supporting that SEQ ID NO: 7 was a newly identified exon of XM_051857.1 was the identification of a 3' end 'ga' splicing site.

KIAA1199 encodes a primary transcript which is protein encoding

a. At the time of the corresponding PCT application was filed (September 2002), a new version of the Genome database was available (Hg9) which now defined a single transcript from the gene locus to which SEQ ID NO: 7 had 99.8% sequence identity. Thus it would have been straightforward for the skilled artisan to determine that the incomplete cDNA clone, named SEQ ID NO: 7, belonged to the gene predicted in chr 15 of Hg8: 82400000-8260000, a gene which was later named KIAA1199.

b. In 2001 it was routine to demonstrate that the identified potential 3' end splicing site just outside the 3'-end boundary of SEQ ID NO: 7 was spliced to the 5' end of downstream exon of XM_051857.1 (in this cDNA clone that was exon 2). This could have been done using a radioactive labelled probe of SEQ ID NO: 7 followed by a Northern blotting analysis of crude transcriptome extract from neoplastic colon tissue specimens. Another alternative routine method was to use conventional PCR with a forward primer in the 3' end of SEQ ID NO: 7 and a reverse primer in the 5' end of the downstream exon 2 of XM_051857.1. Such an example was provided in the Pedersen Declaration (previously submitted), Example 3, where the obtained PCR product demonstrated that SEQ ID NO:7 is part of the KIAA 1199 transcript.

KIAA1199 encodes a primary transcript which is protein encoding

a. The SEQ ID NO: 7 5' end is not a classic 5' end splicing site. At the filing of the provisional application, it was concluded that SEQ ID NO: 7 represented an alternative first exon. Complex 5'UTRs are found in 10% of mRNAs and often in those encoding regulatory proteins such as proto-oncogenes and growth factors (see, e.g., Willis, *Int J. Biochem Cell Biol.* 31: 73-86, 1999; an der Velden et al., *Int J. Biochem Cell Biol.* 31: 87-106, 1999).

b. One skilled in art it would have concluded that SEQ ID NO: 7 was part of an oncogene and SEQ ID NO: 7 represented an alternative 5' UTR which is included in a neoplastic transcript derived from XM_051857.1. Such conclusion was further supported by the

recognition of the first exon of XM_051857.1 not containing any start codons.

c. As neither SEQ ID NO: 7 nor the other identified cDNA clones in the predicted gene locus defined by the boundaries of the clone XM_051857.1 contain the characteristics of non-coding RNAs, miRNA, snoRNA, rRNA, tRNA, URNAs, small nuclear RNA or small non mRNAs[7], which all are defined by clearly recognized motifs and short RNAs, it was clear that the long SEQ ID NO: 7 (>3000nt) transcript and the even longer XM_051857 cDNA clone was representing a true mRNA.

d. Using the online tools through Swissprot in 2001 it was routine to identify the open reading frame. A person skilled in the art would have identified 10 small ORFs (8 ORFs of about 50 amino acid residues and two of about 150 amino acid residues). One skilled in the art would have concluded that SEQ ID NO: 7 represented a neoplastic 5' UTR with classic uORFs previously described (see, e.g., Willis (1999), *supra*; an der Velden et al. (1999), *supra*).

e. The longest encoding reading frame was routine to detect starting from the exon downstream of SEQ ID NO: 7, of which an ATG located 17 bp downstream of the 5' end of exon 2 in XM_051857.1 would result in a 1361 amino acid peptide.

f. It was routine in 2001 to demonstrate that a protein was indeed produced from the gene locus defined by XM_051857.1 cDNA by, for example:

   i. using an *in vitro* system such as rabbit reticulocytes, wheat germ, bacterial system or by transient transfection system. By using ^{35}S-labelled methionine it was routine to verify that a protein was synthesized from a clone containing SEQ ID NO:7 or the complete transcript from the gene of interest by running the subsequent crude protein extracts on SDS_PAGE; or

   ii. using a peptide segment of any of the predicted ORFs in either SEQ ID NO: 7 or the 1361 aa resulting from XM_051857.1 as an immunogen for production of polyclonal antibody, which then could be used in a routine Western blotting

analysis of crude extracts from either one of the in vitro systems described above or using a crude protein extract from neoplastic colon tissue specimen.

g. In terms of whether an increase in mRNA levels corresponded to an increase in translation product, a large fraction of the transcriptome correlates between mRNA abundance and cognate protein abundance. Therefore one skilled in the art would have reasonably concluded that an increase in mRNA levels would result in an increase protein levels as well.

The gene products could be detectable extracellularly.

a. In 2001 it was well documented that the mean feature of secreted proteins was the existence of a signal sequence/signal peptide (*Proteins: Structure, Function, and Bioinformatics*, vol 42(1): 136-138, Jan 2001). A person skilled in the art in 2001 would have been able to use signal peptide prediction software such as those available through Expasy to demonstrate a strong indication of a signal peptide sequence in the 1361 aa predicted protein.

b. It was routine to demonstrate whether a gene of interest encoded a secreted protein by using a polyclonal antibody produced as described above in a Western blotting analysis of culture supernatant of transient transfected cells expressing KIAA1199 or a Western Blotting analysis of blood.

c. With regard to detecting extracellular RNA derived from KIAA1199 in 2001, the literature already described the existence of tumor mRNA or DNA in serum, plasma and blood from patients with cancers (Kopreski et al., *Clin Cancer Res* 5: 1961-1965 (1999); Hasselman et al., Oncol Rep 8:115-18 (2001); Sozzi et al., *Cancer Research* 61:4675-4678 (2001)); therefore it was reasonable to expect that measuring KIAA1199 RNA, DNA or protein in blood has diagnostic utility.

In respect to Figure 1 in Exhibit 3 of the Pedersen Declaration (previously submitted)

which the Examiner questioned, it is submitted that the example provided was based on the Examiner's request to demonstrate an up-regulated activity across all of the KIAA1 199 annotated genome. The request followed earlier correspondence in which this figure showed a custom made microarray (made by Affymetrix and believed to contain probes targeting SEQ ID NO:7) which showed SEQ ID NO: 7 as up-regulated. Figure 1 in the Pedersen Declaration was to show that publically known exonic segments in KIAA1199 are also up-regulated. Although this is exemplified using techniques available subsequent to 2001, the data in the figure support the fact that SEQ ID NO: 7 is a segment of KIAA1199 and that the whole gene is up-regulated in neoplasia. In 2001 one skilled in the art would have been able to demonstrate the same by PCR using primers and the exon-exon junction.

In respect to the Galamb et al. reference, the Examiner has chosen to look at the relatively few markers that did not show an up-regulation in blood as measured in tissue samples, rather than at the main fraction of markers which did show a correlation. At the time the provisional application was filed in 2001, routine assays such as immunoassays, Western blotting, or RT PCR based on protein or RNA extracts from either neoplastic tissue specimens or blood specimens were available, and one skilled in the art would have been able to conduct appropriate analysis.

In view of the foregoing, it is respectfully submitted that those skilled in the art would have been able to practice the claimed method without undue experimentation. Therefore, the present method is fully enabled by the specification in full compliance with 35 U.S.C. §112, first paragraph. Withdrawal of the enablement rejection is therefore respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited

Respectfully submitted,

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Enc. Supporting references cited herein together with an IDS.